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## Factors associated with outcome of liver surgery and hepatocellular carcinoma

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# CHAPTER 4

## **IMMEDIATE POSTOPERATIVE LOW PLATELET COUNT IS ASSOCIATED WITH DELAYED LIVER FUNCTION RECOVERY AFTER PARTIAL LIVER RESECTION**

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**ABSTRACT**

**OBJECTIVE:** To evaluate whether a low postoperative platelet count is associated with a poor recovery of liver function in patients after partial liver resection.

**Background:** Experimental studies in rodents have recently suggested that blood platelets play a critical role in the initiation of liver regeneration. It remains unclear whether platelets are also involved in liver regeneration in humans.

**METHODS:** In a series of 216 consecutive patients who underwent partial liver resection for colorectal liver metastases, we studied postoperative mortality and liver dysfunction in relation to the immediate postoperative platelet count. All patients had normal preoperative liver function and none of them had liver fibrosis or cirrhosis. Delayed postoperative recovery of liver function was defined as serum bilirubin  $> 50 \mu\text{mol/L}$  or prothrombin time  $> 20$  seconds at any time point between postoperative day 1 and 5.

**RESULTS:** Patients with a low ( $<100 \times 10^9/\text{L}$ ) immediate postoperative platelet count had worse postoperative liver function, higher serum markers of liver injury, and increased mortality compared with patients with normal platelet counts ( $\geq 100 \times 10^9/\text{L}$ ). A low immediate postoperative platelet count was identified as an independent risk factor of delayed postoperative recovery of liver function (OR, 11.5; 95% CI, 1.1–122.4;  $P = 0.04$  in multivariate analysis).

**CONCLUSION:** After partial liver resection, a low platelet count is an independent predictor of delayed postoperative liver function recovery and is associated with increased risk of postoperative mortality. These clinical findings are in accordance with the accumulating evidence from experimental studies, indicating that platelets play a critical role in liver regeneration.

## INTRODUCTION

Partial liver resection has become the treatment of choice for patients with colorectal liver metastasis.<sup>1-4</sup> Although resection related mortality and morbidity has decreased substantially in recent years, postoperative mortality rate may still be as high as 1% to 5%.<sup>5-10</sup> Morbidity and mortality are, among other factors, strongly related to postoperative liver insufficiency, which may be a consequence of failure of liver regeneration due to underlying liver disease or insufficient volume of residual functional hepatic reserve.<sup>11</sup>

Liver regeneration requires an orchestrated interplay of cytokines and growth factors, resulting in a time-dependent replication of different types of liver cells.<sup>12</sup> Experimental studies suggest that blood platelets play a pivotal role in liver regeneration after partial liver resection.<sup>13-16</sup> Depletion of platelets severely suppresses liver regeneration, whereas induction of thrombocytosis by administration of thrombopoietin or by splenectomy has been shown to accelerate liver regeneration.<sup>13-15</sup> There is evidence that platelet-derived serotonin plays an essential role in platelet-mediated liver regeneration.<sup>14</sup>

Although the role of platelets and platelet-derived serotonin on hepatocyte proliferation has been established in vitro and in murine models, it is not known whether similar mechanisms apply in humans. Previous studies have identified an association between preoperative platelet count and outcome after liver resection, but these studies were performed in heterogeneous patient populations, including a considerable proportion of patients with chronic liver disease and subsequent thrombocytopenia due to portal hypertension and hypersplenism.<sup>8,17-19</sup> Moreover, these studies did not consider the number of platelets immediately after surgery, when liver regeneration is initiated. These studies, therefore, do not allow an unbiased assessment of the possible relationship between platelets and liver regeneration in humans.

We here report a clinical study in which we examined the relationship between immediate postoperative platelet count and outcome after partial liver resection in patients without preexisting liver disease, specifically in patients with colorectal liver metastases. We hypothesized that patients with a low immediate postoperative platelet count, ie, at the moment when liver regeneration starts, would have a less effective liver regeneration as compared with those with a normal platelet count. We evaluated whether an immediate postoperative low platelet count was associated with poor recovery of liver function and higher risk of mortality. Primary outcome parameters were 90-day postoperative mortality, postoperative liver dysfunction, and postoperative serum markers of liver injury. In addition, we performed a uni- and multivariate analysis to identify clinical variables that are associated with delayed postoperative recovery of liver function.

## PATIENTS AND METHODS

### STUDY POPULATION

A total of 533 consecutive liver resections were performed at the Department of Surgery of university Medical Center Groningen between January 1995 and September 2007. Only patients who underwent liver resection for colorectal liver metastasis and who did not have a preexisting liver disease (n=232) were selected for the current study. Sixteen patients were subsequently excluded from the analysis because platelet count at the day of operation was not documented. This resulted in a total of 216 patients included in the study. The baseline characteristics of the patients and variables related to the perioperative management and surgical procedure were obtained from a prospectively collected database. When necessary, the computer-stored hospital files were reviewed for other relevant clinical parameters and missing laboratory data. Patient characteristics and surgical variables for the entire series are presented in Table 1. The percentage of resected functional liver volume was calculated from published estimates of the proportion of liver volume of each individual segment.<sup>20,21</sup> Specifically, we have used the following subdivision: segment 1 represents 2% of total liver volume, segment 2: 8%, segment 3: 8%, segment 4: 17%, segment 5: 17.5%, segment 6: 15%, segment 7: 15%, segment 8: 17.5%. National legislation and the ethical committee of our institution approve this type of retrospective studies.

### LABORATORY VARIABLES

To study the possible role of platelets in liver regeneration, we identified the immediate postoperative platelet count in each individual patient. Platelet count was always obtained at the day of the surgery, usually upon arrival at the intensive care unit (ICU) after surgery. On the basis of this platelet count, patients were divided into 2 groups: patients with a low platelet count ( $<100 \times 10^9/L$ ) and patients with a normal platelet count ( $\geq 100 \times 10^9/L$ ). In addition, the following laboratory variables were included in the analyses: serum levels of total bilirubin, creatinine, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), hemoglobin, and gamma-glutamyltransferase (GGT) as well as prothrombin time (PT) and plasma levels of antithrombin (AT). Laboratory data were obtained on day 0 (immediately after surgery), between postoperative day 1 and 3, between day 4 and 6, between day 7 and 10, between day 11 and 20, and between day 21 and 30.

### OUTCOME PARAMETERS

The following outcome parameters were considered in this study: mortality within 90 days after surgery and delayed postoperative recovery of liver function. Delayed recovery of liver function was used as a surrogate marker for poor liver regeneration. The definition of delayed postoperative recovery of liver function was based on a modification of the criteria suggested by Balzan et al.<sup>10</sup> and included serum bilirubin  $> 50 \mu\text{mol/L}$  or PT  $> 20$  seconds at any time

**Table 1:** Comparison of patient characteristics and surgical variables in patients with low (<100 x 10<sup>9</sup>/L) or with high (≥100 x 10<sup>9</sup>/L) platelet count after partial liver resection.

Variables	Total (n=216)	Low Platelet Count (n=21)	High Platelet count (n=195)	P
<b>Patient variables</b>				
Age (yr), median (IQR)	67 (59–74)	71 (67–75)	66 (59–74)	0.03
Sex, man	125 (58%)	13 (62%)	112 (58%)	0.82
Location of primary tumor				0.35
Colon	135 (63%)	11 (50%)	124 (64%)	
Rectum	81 (37%)	10 (48%)	71 (36%)	
Timing of metastasis				0.62
Synchronous	65 (30%)	5 (24%)	60 (31%)	
Metachronous	151 (70%)	16 (76%)	16 (76%)	
<b>Comorbidity</b>				
Diabetes mellitus, yes	14 (7%)	0	14 (7%)	0.37
Cardiovascular disease, yes	18 (8%)	3 (14%)	15 (8%)	0.39
Hypertension, yes	30 (14%)	0	30 (15%)	0.05
COPD, yes	8 (4%)	1 (5%)	7 (4%)	0.67
Preoperative chemotherapy, yes	77 (36%)	8 (38%)	69 (35%)	0.81
Previous liver surgery, yes	9 (4%)	0	9 (5%)	0.61
<b>Surgical variables</b>				
Liver volume removed	213/216*			0.67
<35%	89 (42%)	7 (33%)	82 (43%)	
35%–65%	84 (39%)	10 (48%)	74 (38%)	
>65%	40 (19%)	4 (19%)	36 (19%)	
Blood loss	197/216*			<0.01
>1000 mL	109 (55%)	5 (23%)	104 (59%)	
1000–5000 mL	81 (41%)	11 (52%)	70 (40%)	
>5000 mL	7 (4%)	5 (23%)	2 (1%)	
RBC transfusion, yes	215/216*	77 (36%)	19 (91%)	<0.01
Length of stay in ICU				0.02
≤2 days	148 (68%)	10 (48%)	138 (71%)	
3–5 days	43 (20%)	5 (24%)	38 (19%)	
>5 days	25 (12%)	6 (28%)	19 (10%)	
Length of hospital stay				0.07
≤15 days	116 (54%)	7 (33%)	109 (56%)	
>15 days	100 (46%)	14 (67%)	86 (44%)	
<b>Preoperative laboratory values</b>				
AST (U/L), median (IQR)	189/216*	28 (24–40)	29 (23–37)	0.98
ALT (U/L), median (IQR)	190/216*	23 (15–37)	24 (17–31)	0.62
GGT (U/L), median (IQR)	171/216*	38 (24–62)	44 (30–87)	0.24
Hb (mmol/L), median (IQR)	200/216*	8.6 (7.9–9.2)	8.6 (8.0–9.2)	0.69
Albumin (g/L), median (IQR)	170/216*	44 (39–46)	43 (40–45)	0.90
TB (μmol/L), median (IQR)	187/216*	12 (10–16)	11 (8–14)	0.12
AT (%), median (IQR)	154/216*	86 (72–102)	100 (88–112)	<0.01
PT (s), median (IQR)	164/216*	13.2 (12.6–14.2)	12.6 (11.6–13.2)	0.01
Creatinine (μmol/L), median (IQR)	216/216	86 (73–96)	82 (73–95)	0.59

\*Some variables were not available for all patients. Indicated are the numbers of patients for whom values were available. ALT indicates alanine aminotransferase; AT, antithrombin; AST, aspartate aminotransferase; Hb, hemoglobin; ICU, intensive care unit; IQR, interquartile range; GGT, gamma-glutamyltransferase; PT, prothrombin time; RBC, red blood cells; TB, total bilirubin

point between postoperative day 1 and postoperative day 5. Hemolytic or obstructive mechanisms for high bilirubin levels were excluded. Based on these criteria, 123 patients were categorized as having adequate postoperative liver function recovery, and 93 were categorized as having delayed postoperative liver function recovery. Clinical and laboratory variables of the 2 groups were compared.

## STATISTICAL ANALYSIS

Statistical analyses were performed using the statistical software package SPSS 14.0 (SPSS Inc, Chicago, IL). Categorical variables were presented as numbers and percentages, and groups were compared using the Pearson  $\chi^2$  test or Fisher exact test. Continuous variables were expressed as median and interquartile range (IQR), and groups were compared using the Mann-Whitney U test. Uni- and multivariate logistic regression analysis was used to identify independent risk factors for delayed postoperative liver function recovery and odds ratios (OR) with the corresponding 95% confidence intervals (95% CI) were calculated. The following variables were included in these analyses: age, sex, location of primary carcinoma, timing of metastasis, comorbidities, chemotherapy, first or second liver resection, volume of segments resected, intraoperative blood loss, perioperative red blood cell (RBC) transfusion, length of stay in the intensive care unit and hospital, and preoperative laboratory parameters. Preoperative laboratory parameters were assessed within 5 days prior to surgery. All variables that reached a  $P \leq 0.1$  in the univariate analysis were included in the multivariate logistic regression analysis.  $P < 0.05$  was considered statistically significant.

## RESULTS

### COMPARISON OF PATIENTS WITH LOW AND NORMAL POSTOPERATIVE PLATELET COUNT

Of the total of 216 patients included in this study, 21 patients had a low platelet count ( $<100 \times 10^9/L$ ) immediately after surgery, while 195 patients had a normal platelet count ( $\geq 100 \times 10^9/L$ ). A comparison of patient demographics and clinical variables in these 2 groups is presented in Table 1. Patients with a low postoperative platelet count were slightly older, had more perioperative blood loss, received more RBC transfusions, and had a longer postoperative stay in the ICU. Other important variables, such as the number of resected liver segments and preoperative laboratory values, were similar between the 2 groups, except for a slightly decreased AT and slightly longer PT in the group with a low platelet count.

### IS LOW POSTOPERATIVE PLATELET COUNT ASSOCIATED WITH INCREASED MORTALITY?

Overall mortality within 90 days after surgery for the entire series of patients was 4.7%. Mortality rate within 90 days after surgery was almost 4 times higher in patients with a low postoperative platelet count, compared with patients with a normal platelet count (OR, 3.9; 95% CI, 0.95–15.99,  $P = 0.06$ ). A formal multivariate analysis of this outcome parameter could not be performed due the low number of patients who died postoperatively.

### IS LOW POSTOPERATIVE PLATELET COUNT ASSOCIATED WITH BIOCHEMICAL EVIDENCE OF INCREASED LIVER INJURY AND DYSFUNCTION?

Perioperative evolution of biochemical markers of liver cell injury and dysfunction are presented in Figure 1. Postoperatively, peak levels of AST and ALT were significantly higher

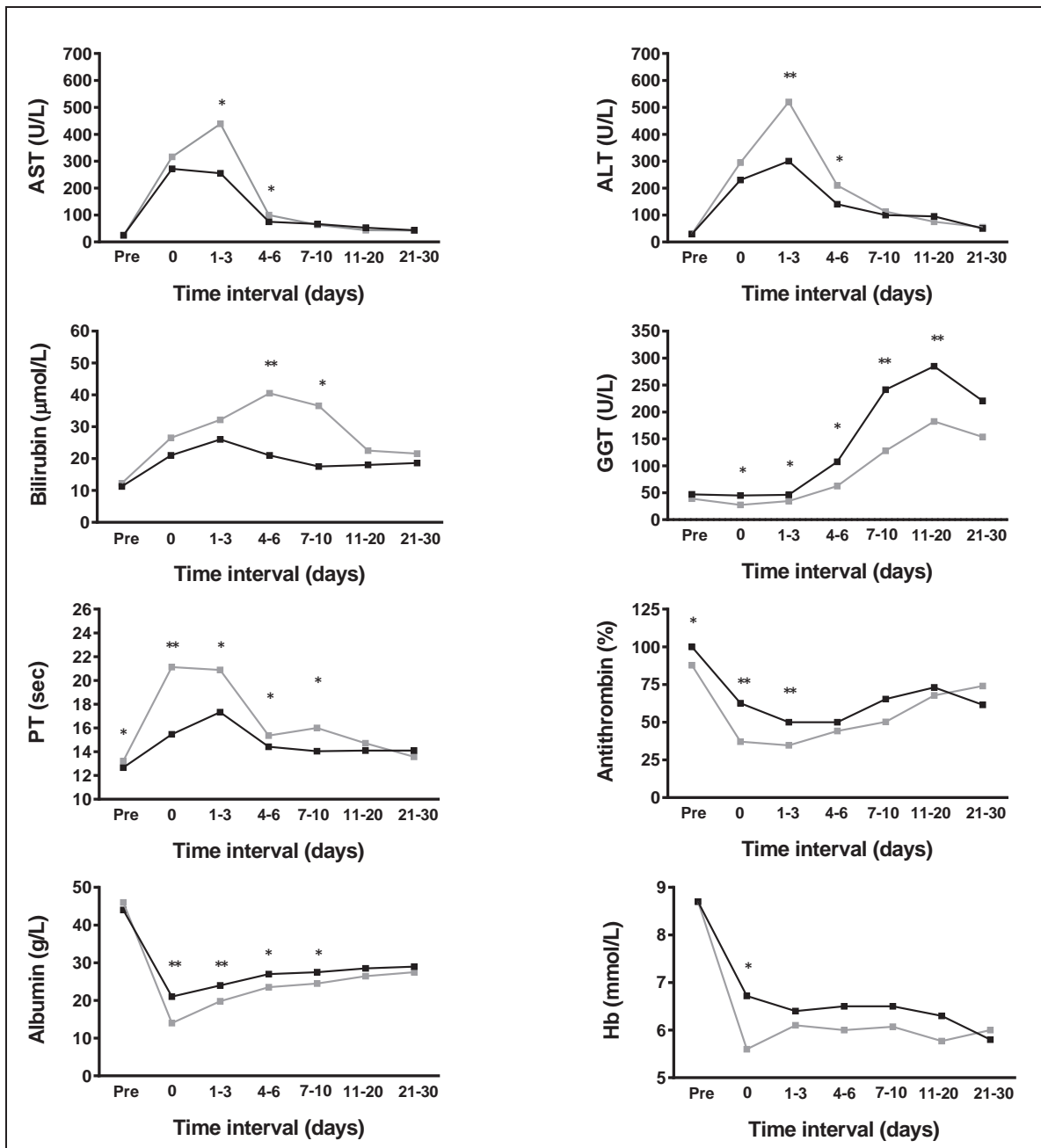


Figure 1: Evolution of laboratory variables in patients with low (gray lines,  $<100 \times 10^9/L$ ) and normal (black lines,  $\geq 100 \times 10^9/L$ ) immediate postoperative platelet count. Shown are media values. \*\* $P < 0.01$ , \* $P < 0.05$ .

in the patients with a low postoperative platelet count, but values of GGT were lower, compared with patients with normal platelet counts. Patients with a low platelet count had also signs of more delayed recovery of liver function, as illustrated by significantly higher levels of serum bilirubin, higher PT values, and lower levels of AT. Notably, the peak in serum bilirubin level in the group with low platelet counts was observed between day 4 and 6, whereas the peak in the group with normal platelet counts occurred between day 1 and 3. Altogether,



these data suggested that a low platelet count is associated with a more delayed postoperative recovery of liver function.

#### **IS LOW PLATELET COUNT AN INDEPENDENT RISK FACTORS FOR DELAYED POSTOPERATIVE RECOVERY OF LIVER FUNCTION?**

To examine the possible relationship between platelets and recovery of liver function, we next performed a uni- and multivariate analysis of variables that are potentially associated with poor postoperative recovery of liver function. We have used a definition of poor postoperative recovery of liver function that was based on data previously published by Balzan et al<sup>10</sup> and as described above. According to this definition, 93 (43%) patients had delayed postoperative recovery of liver function and 123 (57%) patients had no delayed recovery of liver function. Results of the univariate analysis of potential risk factors for delayed recovery are presented in Table 2. A low platelet count immediately after surgery was associated with an almost 5-fold increased risk of delayed postoperative recovery of liver function (OR, 4.9; 95% CI, 1.7–13.9;  $P < 0.01$ ). Other variables associated with delayed postoperative liver function recovery in the univariate analysis were age, RBC transfusion, the liver volume removed, preoperative levels of serum bilirubin, ALT, GGT, AT, and preoperative PT values. Interestingly, a low preoperative platelet count was not associated with delayed recovery of liver function. Mortality within 90 days after surgery was almost 7-fold higher in patients with delayed postoperative liver function recovery, compared with patients without delayed liver function recovery (OR, 6.5, 95% CI, 1.4–30.8;  $P = 0.02$ ).

Nine variables with a  $P \leq 0.10$  were entered into the multivariate logistic regression analysis. After multivariate analysis, low platelet count remained as a strong and independent risk factor for delayed postoperative recovery of liver function (OR, 11.5; 95% CI, 1.1–122.4;  $P = 0.04$ ) (Table 3). Other variables that were identified as independent risk factors for delayed postoperative liver function recovery were RBC transfusion, liver volume removed, and preoperative serum bilirubin and GGT (Table 3). As RBC transfusion may directly influence postoperative platelet count by hemodilution, we also performed a multivariate analysis without entering RBC transfusions into the model. In this analysis, the risk of delayed postoperative recovery of liver function associated with low platelet count increased to 21.1 (95% CI, 2.2–199.8). Seven patients received a perioperative platelet transfusion. As the biologic characteristics of transfused platelets may differ from that of endogenous platelets, we repeated our analyses with exclusion of these 7 patients, with no significant effect on the risk estimate (data not shown).

#### **DISCUSSION**

This study provides clinical evidence that a low postoperative platelet count is associated with an increased risk of mortality and delayed recovery of liver function after partial liver resections. Furthermore, we have demonstrated that immediately after partial liver resection

**Table 2.** Univariate analysis of risk factors for delayed postoperative recovery of liver function

Variables	No. Patients/No. Patients Analyzed	Delayed Recovery of Liver Function n = 93	OR (95% CI)	P
Age (yr), median (IQR)	216/216	Continuous	1.06 (1.0–1.1)	<0.01
Sex, man	125/216	59 (47%)	1.5 (0.9–2.6)	0.17
Location of primary tumor				0.20
Rectum	81/216	30 (37%)	1.0, Reference	
Colon	135/216	63 (47%)	1.5 (0.8–2.6)	
Timing of metastasis				0.45
Synchronous	65/216	25 (39%)	1.0, Reference	
Metachronous	151/216	68 (45%)	1.3 (0.7–2.4)	
Comorbidity				
Diabetes mellitus, yes	14/216	7 (50%)	1.3 (0.5–4.0)	0.10
Cardiovascular disease, yes	18/216	7 (39%)	0.8 (0.3–2.2)	0.81
Hypertension, yes	30/216	9 (10%)	0.5 (0.2–1.2)	0.12
COPD, yes	8/216	1 (1%)	0.2 (0.2–1.5)	0.11
Preoperative chemotherapy, yes	77/216	36 (47%)	1.3 (0.7–2.2)	0.47
Previous liver surgery, yes	9/216	2 (22%)	0.4 (0.7–1.8)	0.21
RBC transfusion	77/215	53 (69%)	5.6 (3.0–10.2)	<0.01
Liver volume removed				<0.01
<35%	89/213	20 (22%)	1.0, Reference	
35%–65%	84/213	47 (50%)	4.4 (2.3–8.5)	
>65%	40/213	26 (28%)	6.4 (2.8–14.5)	
Blood platelet count on day 0				<0.01
≥100 x 10 <sup>9</sup> /L	195/216	77 (39%)	1.0, Reference	
<100 x 10 <sup>9</sup> /L	21/216	16 (76%)	4.9 (1.7–13.9)	
Preoperative laboratory variables, (tertiles)*				
TB (μmol/L), median (IQR)	187/216			<0.01
Low	63	17 (27%)	1.0, reference	
Intermediate	68	32 (47%)	2.4 (1.2–5.2)	
High	56	33 (59%)	3.9 (1.8–8.4)	
PT (s), median (IQR)	168/216			<0.01
Low	58	18 (31%)	1.0, reference	
Intermediate	59	26 (44%)	1.8 (0.8–3.7)	
High	51	31 (61%)	3.4 (1.6–7.6)	
AST (U/L), median (IQR)	189/216			0.13
Low	65	22 (34%)	1.0, reference	
Intermediate	64	32 (50%)	1.8 (0.8–3.7)	
High	60	29 (48%)	3.4 (1.6–7.6)	
ALT (U/L), median (IQR)	190/216			0.01
Low	67	31 (46%)	1.0, reference	
Intermediate	64	19 (30%)	2.0 (1.0–4.0)	
High	59	33 (56%)	0.8 (0.9–3.8)	
GGT (U/L), median (IQR)	171/216			<0.01
Low	61	21 (34%)	1.0, reference	
Intermediate	53	18 (34%)	0.5 (0.2–1.0)	
High	56	38 (67%)	1.4 (0.7–3.0)	
Albumin (g/L), median (IQR)	170/216			0.70
Low	61	27 (44%)	1.0, reference	
Intermediate	53	24 (45%)	1.0 (0.5–2.2)	
High	56	22 (39%)	0.8 (0.4–1.7)	
AT (%)	154/216			0.01
Low	52	34 (65%)	1.0, reference	
Intermediate	54	24 (44%)	0.4 (0.2–0.9)	
High	48	17 (35%)	0.5 (0.1–1.7)	
Platelet count (100 x 10 <sup>9</sup> /L)	164/216			0.70
Low	57	24 (42%)	1.0, reference	
Intermediate	53	18 (34%)	0.7 (0.3–1.5)	
High	54	22 (41%)	0.9 (0.4–2.0)	
Creatinine (μmol/L), median (IQR)	216/216			0.46
Low	77	29 (38%)	1.0, reference	
Intermediate	67	32 (48%)	1.5 (0.8–2.9)	
High	72	32 (44%)	1.3 (0.9–2.5)	

Abbreviations as in Table 1.

**Table 3.** Multivariate Analysis of Independent Risk Factor for Delayed Postoperative Recovery of Liver Function

Variables	OR 95% (CI)	P
Age	1.00 (0.95–1.06)	0.99
RBC transfusion, (yes vs. no)	6.62 (2.24–19.58)	<0.01
Liver volume removed	2.40 (1.21–4.79)	0.01
Platelet count (<100 x10 <sup>9</sup> /L vs. ≥ 100 x10 <sup>9</sup> /L)	11.49 (1.08–122.41)	0.04
Preoperative serum bilirubin (μmol/L)*	1.19 (1.06–1.33)	<0.01
Preoperative serum GGT (mg/dL)*	1.01 (1.00–1.03)	0.03
Preoperative PT (s)*	1.15 (0.74–1.79)	0.52
Preoperative AT (%)*	0.99 (0.97–1.02)	0.58
Preoperative ALT (U/L)*	1.01 (0.99–1.03)	0.27

\*Preoperative laboratory values were entered as continuous variables in the model. Abbreviations as in Table 1.

patients with low platelet counts have higher serum markers of liver injury (ALT, AST) compared with patients with normal platelet counts. The combined results suggest that a certain number of platelets are required for optimal liver function recovery, presumably mediated by enhancement of liver regeneration. The results of this clinical study are in accordance with data from several experimental studies in rodents suggesting that platelets play a critical role in the initiation of liver regeneration.<sup>14,15</sup> In these experiments, it has been shown that liver regeneration is significantly reduced in mice with severe thrombocytopenia, whereas thrombocytosis is associated with accelerated liver regeneration.<sup>15</sup> Platelet-derived serotonin has been identified as a key mediator of liver regeneration.<sup>14</sup>

Our results are in line with previous clinical studies, suggesting that a low platelet count is associated with poor recovery and worse outcome after liver surgery.<sup>8,17-19,22</sup> However, a major drawback of previous clinical studies has been the inclusion of heterogeneous patient populations, including patients with liver cirrhosis, primary liver cancer, and preexisting thrombocytopenia. It is well known that liver surgery in patients with cirrhosis and primary liver cancer has, in general, a poorer outcome than liver surgery for colorectal liver metastases.<sup>23-25</sup> To avoid possible bias from differences in underlying liver disease, we therefore performed our analyses in a homogenous group of patients with colorectal liver metastases, who did not have any underlying liver disease. Second, we have not investigated the impact of preoperative platelet counts, as was done in most previous studies, but we have used immediate postoperative platelet counts. Liver regeneration is known to be initiated very shortly after partial liver resection,<sup>26</sup> and if platelets are critically involved in this process, the number of platelets available immediately after surgery will be of greater importance than preoperative platelet counts.

After our initial observation that patients with a low postoperative platelet count have an increased risk of mortality, we aimed to study the relation between platelet count and liver regeneration. Unfortunately, we were not able to perform a direct quantification of liver regeneration, which would have required measurements of liver volume by sequential imaging studies in the postoperative phase. Such imaging studies are not routinely performed after partial liver resections in our center. As a surrogate marker of liver regeneration, we therefore used laboratory data of serum markers of liver injury and liver function. Recovery of liver function was assumed to be directly related to adequate liver regeneration.

We have assessed perioperative changes in several laboratory parameters and compared these changes in patients with low or normal postoperative platelet counts. Although there was no difference between the 2 groups in the number of segments removed, patients with a low platelet count had significantly reduced postoperative liver function and a slower recovery of liver function after liver resection. Interestingly, we also observed prominent differences in serum markers of liver injury between the 2 groups. Not only the peak levels of serum transaminases were higher but also the normalization of serum transaminases was more delayed in the group with low platelet counts, compared with the group with normal platelet count. Although these results may suggest that platelets protect against hepatocellular damage induced by liver resection, the higher serum transaminases in the group with low platelet counts may also reflect an impaired capacity of the remaining liver to clear these enzymes from the circulation, since functional liver mass is decreased substantially in the postoperative period.

In a separate analysis, we have subsequently shown that patients with a low platelet count have a significantly higher risk of delayed postoperative recovery of liver function. In fact, in a multivariate regression analysis, the risk of delayed recovery of liver function was more than 11 times higher in patients with a low postoperative platelet count, compared with patients with normal platelet counts. There is no standard definition of delayed postoperative recovery of liver function. Therefore, we have adopted a modified definition based on the criteria proposed by Balzan et al.<sup>10</sup> Delayed recovery of liver function was defined as serum bilirubin > 50  $\mu\text{mol/L}$  and/or PT > 20 seconds at any time during one of the first 5 postoperative days, in the absence of hemolysis or biliary obstruction. According to this definition, a substantial proportion of patients in our study had delayed liver function recovery, and it should be stressed that our definition was not meant to identify patients at a “point of no return” as is achieved with more strict definitions such as the “50–50 criteria” proposed by Balzan et al.<sup>10</sup> or the peak bilirubin > 7 mg/dL (or > 119.7  $\mu\text{mol/L}$ ) as has been proposed by Mullen et al.<sup>9</sup> On the other hand, we did observe a substantially increased risk of mortality in patients that fulfilled our criteria of delayed postoperative liver function recovery.

A limitation of this study is its retrospective design. It cannot be fully excluded that the patients with a low platelet count were simply in a worse general condition and, therefore, had a more delayed recovery of liver function recovery and increased risk of mortality, than patients with normal platelet counts. However, we did not find any major differences in the preoperative characteristics in the 2 groups and also the liver volume removed was similar in the 2 groups. In addition, low platelet count remained as a strong and independent risk factor for delayed postoperative recovery of liver function in the multivariate regression analysis.

The results of this retrospective study require confirmation, but when confirmed, these data may have important clinical implications. If postoperative platelet count is indeed directly related to liver regeneration and recovery of liver function, this would open new avenues to develop novel strategies to stimulate liver regeneration and to avoid liver failure after major liver resections or (partial) liver transplantation. Possible directions could be strategies to increase platelet count, for example, by preoperative administration of thrombopoietin agonists. Based on the finding that platelet-derived serotonin is a key mediator of liver regeneration, an alternative approach could be to use serotonin precursors or serotonin receptor agonists to promote liver regeneration after liver surgery.<sup>14</sup> The current findings should not be seen as a stimulus for a more liberal use of platelet concentrates from blood donors, as several studies have shown that platelet transfusion is associated with an increased risk of postoperative morbidity and mortality.<sup>27-29</sup> In contrast to endogenous platelets, platelets from blood donors are frequently in an activated state and may induce a range of inflammatory reactions and unwanted side effects.<sup>30,31</sup>

In conclusion, this retrospective study suggests that a low platelet count is an independent predictor of delayed postoperative liver function recovery and it is associated with increased risk of postoperative mortality after partial liver resection. These clinical findings are in accordance with the accumulating evidence from experimental studies, indicating that platelets play a critical role in liver regeneration.

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